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Cytomegalovirus Reactivation Following Autologous Peripheral Blood Stem Cell Transplantation for Multiple Myeloma in the Era of Novel Chemotherapeutics and Tandem Transplantation

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Cytomegalovirus (CMV) is an important pathogen after allogeneic transplantation. However, few studies have examined CMV reactivation after autologous peripheral blood stem cell transplantation (APBSCT) to treat multiple myeloma (MM), especially in the setting of the newer chemotherapeutic agents and/or 2 sequential APBSCTs (ie, tandem transplantation). A retrospective chart review of patients with MM who underwent either single APBSCT or tandem transplantation was conducted to evaluate the incidence, risk factors, and outcomes of CMV infection at a single institution. A total of 104 patients with MM underwent transplantation during the study period, including 66 patients who received tandem transplantation. The majority of patients (66 of 104; 63.5%) were CMV-seropositive, and CMV viremia was frequently detected in this subgroup (32 of 66; 48.5%). No primary CMV infections were identified. CMV reactivation was more common in recipients of tandem transplantation than in recipients of single APBSCT ($P < .001$). In addition, patients who developed CMV viremia were more likely to have received conditioning therapy with melphalan, bortezomib, dexamethasone, and thalidomide compared with those without CMV reactivation ($P = .015$). However, on multiple logistic regression analysis, only receipt of tandem transplantation was significantly associated with CMV reactivation (odds ratio, 5.112; 95% confidence interval, 1.27-20.60; $P = .022$). Febrile episodes of CMV viremia were observed in 17 patients (17 of 32; 53.1%), and invasive CMV disease was diagnosed in 1 patient. Our data suggest that CMV reactivation after APBSCT for MM is relatively common, and that viremia is often associated with fever. CMV surveillance should be considered, especially when tandem transplantation is performed using combination chemotherapy with high-dose melphalan.

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INTRODUCTION

Multiple myeloma (MM) accounts for 15% of all new cases of hematologic malignancy diagnosed in the United States each year, with an estimated 21,700 new diagnoses reported annually [1]. The introduction of high-dose chemotherapy with autologous peripheral blood stem cell transplantation (APBSCT) has significantly improved survival rates compared with conventional chemotherapy alone [2]. Recently, additional advances in MM treatment have had a positive impact on both disease-free and overall survival. These advances include the use of novel chemotherapeutic agents (eg, bortezomib, thalidomide, and lenalidomide), as well as more intensive transplantation regimens that involve 2 sequential APBSCTs (ie, tandem transplantation) [3-5]. These treatments also result in a heightened net state of immunosuppression, which increases susceptibility to opportunistic infections [6].

The prevalence of active cytomegalovirus (CMV) infection is lower after conventional single APBSCT than after allogeneic transplantation [7,8]; however, little is known about the overall incidence of active CMV infection in patients with MM receiving more intensive treatment regimens. We performed a retrospective,

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single-center study to evaluate the incidence, risk factors, and outcomes of CMV infection in patients with MM who underwent sequential tandem transplantation with a high-dose melphalan-based regimen combined with novel chemotherapeutics.

PATIENTS AND METHODS

This study involved an Institutional Review Board–approved retrospective review of all patients with MM who underwent APBSCT between October 2007 and February 2009 at the Huntsman Cancer Institute at the University of Utah, a tertiary care, comprehensive cancer facility with an active stem cell transplantation program. Patient data were reviewed for 1 year after single APBSCT or the first APBSCT of a planned tandem transplantation.

Clinical variables included baseline demographic data, such as CMV serostatus (ie, CMV IgG), age, sex, comorbidities, serum creatinine level (>1.4 mg/dL or ≤1.5 mg/dL), multiple myeloma stage as defined by the International Staging System [9], receipt of maintenance chemotherapy within 6 months of the initial APBSCT, history of previous transplantation, preinitial APBSCT $CD4^+$ T cell count, conditioning chemotherapy for both the initial and second APBSCT, occurrence of other microbiologically confirmed bacterial or fungal infections within 30 days of the initial and/or second APBSCT, as well as the duration of neutropenia (defined as an absolute neutrophil count <500 cells/μL).

$CD34^+$-selected peripheral blood stem cells (PBSCs) were mobilized with either recombinant granulocyte colony-stimulating factor (Amgen, Thousand Oaks, CA) alone or chemotherapy (ie, dexamethasone, cisplatin, adriamycin, cyclophosphamide, and etoposide) followed by granulocyte colony-stimulating factor. The conditioning regimens for the initial transplantation consisted of melphalan (M) only; M, bortezomib (B), dexamethasone (D), and thalidomide (T) (M/B/D/T); or M/B/D/gemcitabine (G), with or without carmustine (C) (M/B/D/G+/−C). The latter 2 combinations were also used for the second APBSCT in tandem transplantations. The treating physician selected the conditioning regimen and determined whether the patient underwent single or tandem transplantation.

CMV serostatus was determined for all patients before transplantation using a chemiluminescent immunoassay (Immulite CMV IgG; Siemens, Tarrytown, NY). Routine CMV surveillance was performed weekly after transplantation with an in-house-developed quantitative real-time polymerase chain reaction (PCR) CMV assay (ARUP Laboratories, Salt Lake City, UT). Weekly monitoring was continued until the patient was placed on maintenance chemotherapy, followed by testing every 3 months and/or on the development of signs and symptoms suggesting active CMV infection. The quantitative range of this assay was 2.6-6.6 $\log_{10}$ copies/mL. In the presence of evidence of CMV viremia, as defined by the detection of CMV DNA in 2 sequential plasma specimens, preemptive anti-CMV therapy was initiated at the treating physician's discretion.

Statistical analyses were performed using SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL). Dichotomous variables were compared using the Pearson χ^2 test or Fisher exact test. For continuous variables, the Mann-Whitney *U* test was used. Variables with a *P* value <.20 on comparison analysis were included in a stepwise logistic regression model. Multivariate logistic regression was used to determine factors associated with CMV viremia. Odds ratios and 95% confidence intervals were calculated. A *P* value <.05 was considered to indicate statistical significance.

RESULTS

During the study period, a total of 104 patients with MM were treated with APBSCT. The study population was predominantly white (92.3%) and male (72.1%), and had a median age of 61 years (interquartile range [IQR], 53-67). The majority of patients (93 of 104; 89.3%) received dexamethasone, cisplatin, adriamycin, cyclophosphamide, and etoposide chemotherapy for PBSC mobilization. Thirty-eight patients (36.5%) underwent single APBSCT using of one of the following conditioning regimens: M alone (n = 5), M/B/D/T (n = 24), or M/B/D/G+/−C (n = 9). The remaining 66 patients (63.4%) underwent tandem transplantation using M alone (n = 2), M/B/D/T (n = 63), or M/B/D/G+/−C (n = 1) as conditioning for the first transplantation and either M/B/D/T (n = 59) or M/B/D/G+/−C (n = 7) for the second transplantation. The median time between the first and the second transplantation of a tandem APBSCT was 88 days (IQR, 81-101 days).

Sixty-six of the 104 patients (63.4%) were CMV IgG-positive before APBSCT. No cases of primary CMV infection were identified among the CMV-seronegative patients during the first year after APBSCT. Overall, 48.5% (32 of 66) of CMV-seropositive patients developed at least one episode of CMV viremia. Active CMV infection developed in 18.2% (4 of 22) of the seropositive single APBSCT recipients, compared with 63.6% (28 of 44) of the tandem APBSCT recipients, a statistically significant difference in proportion ($P < .001$). Of the patients who underwent tandem transplantation, 11 (25%) developed CMV viremia after the first transplantation, 9 (20.5%) did so after the second transplantation, and 8 (18.2%) did so after both transplantations. The time from stem cell infusion to the development of CMV viremia ranged from 8 days to 26 days.

CMV-seropositive patients were categorized by reactivation status for comparison analysis (Table 1). Tandem transplantation and receipt of M/B/D/T were more common in the patients who developed CMV reactivation than in those who did not ($P < .001$ and .015, respectively). There was an inverse relationship between a history of previous APBSCT and CMV reactivation. A history of previous APBSCT for MM was less common in patients with CMV reactivation than in those without CMV reactivation (3 of 32 [9.4%] versus 15 of 34 [44.1%]; $P = .002$). Among the 18 patients with a previous APBSCT, 10 received a single APBSCT and 8 underwent tandem transplantation during the study period. The median time between previous APBSCT and the initial transplantation of this study was 30 months (IQR, 21-50 months). There were no significant differences in the duration of neutropenia, presence of other confirmed bacterial or fungal infections, or all-cause mortality between patients with and those without CMV reactivation. Multiple logistic regression analysis was performed using variables with a P value <.20 on comparison analysis (Table 2). In this model, only receipt of tandem transplantation was significantly associated with CMV reactivation (odds ratio, 5.11; 95% confidence interval, 1.27-20.60; $P = .022$).

CMV reactivation was further classified according to the timing of onset of viremia (Table 3). Group 1 reactivated CMV after a single APBSCT (n = 4), group 2 reactivated CMV only after the first transplantation of a tandem APBSCT (n = 11), group 3 reactivated CMV only after the second transplantation of a tandem APBSCT (n = 9), and group 4 reactivated CMV after both the first and the second transplantations of a tandem APBSCT (n = 8). The median duration of neutropenia and other infectious complications were similar across the 4 groups. Median peak CMV DNA was highest after the second transplantation, especially in those patients with reactivated CMV after the first transplantation.

Approximately one-half of the patients with viremia (17 of 32; 53.1%) developed fever without any other identifiable cause (ie, CMV syndrome). Although there was a trend toward higher peak DNA loads in patients with CMV syndrome compared with asymptomatic patients (median, 3.6 $\log_{10}$ copies/mL [IQR, 3.3-4.2 $\log_{10}$ copies/mL] versus 3.4 $\log_{10}$ copies/mL [IQR, 3.1-4.0 $\log_{10}$ copies/mL]), this trend was not statistically significant (Figure 1). Peak CMV DNA loads were higher in the patients who were treated for CMV reactivation than in those not treated (median, 3.6 $\log_{10}$ copies/mL; [IQR, 3.3-4.3 $\log_{10}$ copies/mL] versus 3.3 $\log_{10}$ copies/mL [IQR, 3.0-3.7 $\log_{10}$ copies/mL]; $P = .056$) (Figure 2). In addition, persistent viremia (ie, detectable CMV DNA load in more than 2 sequential plasma specimens) was more prevalent in treated patients compared with untreated patients. Of note, no untreated patient had evidence of a persistently positive sequential CMV DNA viral load in plasma specimens.

Table 1. Characteristics of the CMV-Seropositive Patients*

	CMV Nonreactivation (n = 34; 51.5%)	CMV Reactivation (n = 32; 48.5%)	P
Previous APBSCT, n (%)	15 (44.1)	3 (9.4)	.002
Chemotherapy within previous 6 months, n (%)†	16 (47.1)	13 (40.6)	.599
Age, years, median (IQR)	62 (53-68)	62 (54-68)	.959
Males, n (%)	24 (70.6)	19 (59.4)	.339
Females, n (%)	10 (29.4)	13 (40.6)	
Other medical conditions, n (%)			
HIV or solid organ transplant recipient	0 (0.0)	1 (3.1)	.485
Diabetes mellitus	4 (11.8)	4 (12.5)	1.000
Renal insufficiency‡	3 (8.8)	2 (6.3)	1.000
MM disease stage, n (%)			
Stage 1	8 (23.5)	4 (12.5)	.246
Stage 2	8 (25.5)	6 (18.8)	.635
Stage 3	18 (52.9)	22 (68.8)	.189
$CD4^+$ T cell count, median (IQR)	153 (87-367)	212 (133-320)	.334
Conditioning regimen, n (%)			
M	4 (11.8)	2 (6.3)	.673
M/B/D/T	24 (70.6)	30 (93.8)	.015
M/B/D/G+/−C	6 (17.6)	0 (0.0)	.025
Duration of neutropenia, days, median (IQR)§	8 (7-8)	8 (6-9)	.635
Other infection within 30 days, n (%)‖	12 (35.3)	15 (46.9)	.339
Tandem autologous stem cell transplantation, n (%)	16 (47.1)	28 (87.5)	<.001
Overall mortality, n (%)¶	3 (8.8)	3 (9.4)	1.000

*Age, other medical conditions, MM disease stage, and median $CD4^+$ cell count reflect baseline characteristics at single or first APBSCT of tandem transplantation.
†Receipt of chemotherapy in the 6 months before transplantation for indications other than stem cell collection.
‡Renal insufficiency defined as serum creatinine >1.5 mg/dL.
§Neutropenia defined as absolute neutrophil count <500 cells/μL after single or first APBSCT of tandem transplantation.
‖Confirmed bacterial or fungal infection within 30 days of single or first APBSCT of tandem transplantation.
¶Death from any cause by the end of 1-year follow-up.

Table 2. Multiple Logistic Regression Analysis of Variables Associated with CMV Reactivation

	Odds Ratio	95% Confidence Interval	P
Previous APBSCT			
No (reference)			
Yes	0.259	(0.055-1.213)	.086
MM disease stage			
1 (reference)			
2	0.970	(0.153-6.163)	.974
3	1.904	(0.383-9.456)	.431
Conditioning regimen			
M (reference)			
M/B/D/T	1.839	(0.223-15.195)	.572
M/B/D/G+/−C	0.000	(0.000-0.000)	.999
Tandem APBSCT			
No (reference)			
Yes	5.112	(1.269-20.595)	.022

Table 3. CMV Reactivation Stratified by the Timing of Viremia and Type of APBSCT

	Group 1 (n = 4)	Group 2 (n = 11)	Group 3 (n = 9)	Group 4 (n = 8)	
				First APBSCT	Second APBSCT
Time to viremia, days, median (IQR)*	13 (3-27)	8 (6-13)	26 (19-34)	10 (6-16)	24 (19-27)
Duration of neutropenia, days, median (IQR)†	10 (7-10)	8 (7-10)	7 (6-8)	6 (5-8)	7 (6-8)
Other infection within 30 days, n (%)‡	2 (50.0)	7 (63.6)	2 (22.2)	4 (50.0)	4 (50.0)
Peak CMV DNA viral load, $\log_{10}$ copies/mL, median (IQR)	3.4 (2.9-3.9)	3.7 (3.2-3.9)	3.1 (2.9-3.6)	3.5 (3.4-4.3)	4.3 (3.6-4.6)
CMV viremia associated with fever, n (%)	2 (50.0)	5 (45.5)	5 (55.6)	5 (62.5)	3 (37.5)
Biopsy-proven invasive CMV disease, n (%)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)
CMV treatment, n (%)[8]					
No treatment	1 (25.0)	2 (18.2)	4 (44.4)	3 (37.5)	0 (0.0)
Ganciclovir/valganciclovir	3 (75.0)	9 (81.8)	5 (55.6)	3 (37.5)	7 (87.5)
Foscarnet	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	1 (12.5)

Group 1: CMV reactivation after single APBSCT; group 2: CMV reactivation after the first APBSCT of tandem transplantation; group 3: CMV reactivation after the second APBSCT of tandem transplantation; group 4: CMV reactivation after both the first and the second APBSCTs of tandem transplantation.
*Time from transplantation to development of CMV reactivation.
†Neutropenia is defined as an absolute neutrophil count <500 cells/μL.
‡Confirmed bacterial or fungal infection within 30 days of APBSCT.

The majority of patients with viremia (25 of 32; 78.1%) were successfully treated with valganciclovir, ganciclovir, or foscarnet. Invasive colitis was diagnosed in 1 patient (of group 3). In addition, there was a molecularly confirmed case of drug-resistant CMV infection in a patient who had also undergone kidney transplantation. None of the patients with untreated viremia developed identifiable CMV sequelae.

DISCUSSION

CMV establishes lifelong latency within host cells. Various populations of $CD4^+$ and $CD8^+$ T cells, as well as natural killer (NK) cells, are essential to controlling this infection [10-12]. In the setting of impaired cellular immunity, CMV may reactivate from latency, disseminate, and directly cause life-threatening disease [13,14]. The virus also encodes multiple proteins that specifically target and counteract the host immune response [15]. Based on these immunomodulatory properties, CMV is thought to indirectly promote the development of other opportunistic infections and allograft rejection in some patients [16].

Previous studies that included $CD34^+$-selected autologous transplantation recipients reported an overall incidence of active CMV infection of 26%-39% [17,18]. We found a much higher overall rate in the present study (48.5%), including a rate of 63.6% in seropositive patients who underwent tandem transplantation with a newer combination chemotherapy regimen. There are several potential explanations for the higher prevalence of active CMV infection in our patient population. First, in older studies, routine CMV surveillance was done using the pp65 antigenemia assay [17,18], a less-sensitive laboratory method than real-time PCR. In addition, the use of newer chemotherapeutic agents as a part of the conditioning regimen likely has a greater impact on CMV-specific T cell immunity than the use of melphalan

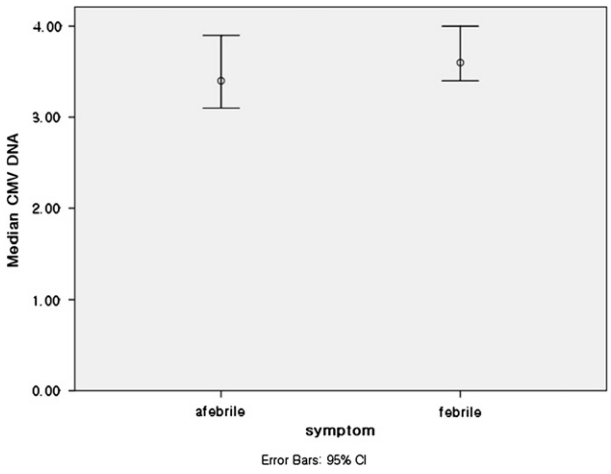

Figure 1. Comparison of median peak CMV DNA viral loads ($\log_{10}$ copies/mL) in symptomatic and asymptomatic patients with viremia.

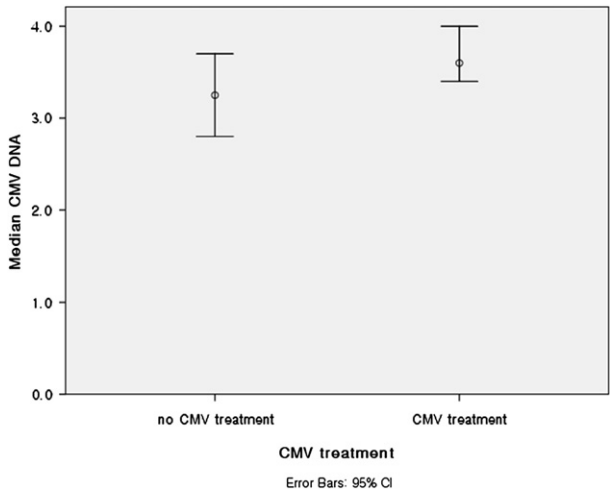

Figure 2. Comparison of median peak CMV DNA viral loads ($\log_{10}$ copies/mL) in untreated and treated patients with viremia.

alone. In terms of chemotherapeutic effects, melphalan is associated with bone marrow suppression, including neutropenia [19], and decreased numbers of T lymphocytes, including $CD4^+$ T cells [20]. Along with causing neutropenia, bortezomib diminishes the proliferation and function of $CD8^+$ T lymphocytes as well as NK cells [21]. A previous study found a higher incidence of varicella zoster virus infection in patients treated with bortezomib [22]. Extrapolating from these observations suggests that bortezomib use also likely contributed to the high prevalence of CMV reactivation seen in our study population. Dexamethasone is well recognized for its effects on cell-mediated immunity through the inhibition and modulation of IL-2, a principal T cell growth factor [23,24], as well as through the induction of cellular apoptosis [25]. Thalidomide has both immunostimulatory and immunomodulatory properties, which include activation of virus-specific $CD8^+$ T cells and NK cells [26,27]. The addition of thalidomide to other agents does not appear to increase or decrease the risk of infection in MM patients, however [28]. Finally, the cumulative immunosuppression resulting from tandem transplantation might additively impact host susceptibility to CMV. This possibility is supported by our finding that more than one-half (53.1%) of CMV reactivations occurred after the second of 2 sequential transplantation. Receipt of a previous APBSCT was not identified as a significant risk factor for CMV reactivation, however, suggesting that recent immunosuppression may be more important than a remote history of previous transplantation.

CMV reactivation was often associated with fever, but biopsy-proven invasive disease and/or the development of genotypic drug resistance was rare. The low rates of CMV disease and treatment failure owing to drug resistance likely reflect the overall efficacy of prompt preemptive antiviral therapy. None of the 7 patients with untreated CMV reactivation developed clinical signs or symptoms of invasive disease. Untreated patients also tended to have lower CMV DNA viral loads than treated patients; however, the substantial overlap in CMV DNA levels between treated and untreated patients precluded us from determining an optimal CMV DNA viral load threshold for preemptive treatment. Additional work is needed to identify those patients with MM most likely to benefit from early antiviral therapy.

This study has several limitations. First, the combination of M/B/D/G+/−C likely has significant T cell immunosuppressive effects; however, use of this conditioning regimen was not associated with CMV reactivation in this study. Sampling bias introduced by the small number of patients who received M/B/D/G+/−C is likely. The patients with MM were treated according to physician preference, which might have introduced a selection bias. As a result, comparisons of regimens might be imbalanced by patient factors not controlled for in our statistical models. Furthermore, we did not examine CMV-specific immune reconstitution patterns or measure the recovery of NK cell function to test our hypothesis that augmented immunosuppression from combination conditioning regimens, with or without tandem APBSCT, resulted in impaired cellular immunity and an increased rate of CMV reactivation. Previous studies have shown an increase in other bacterial and fungal infections coincident with CMV infection [29], as well as higher peak CMV viral loads in symptomatic patients [30]. Although our data show similar trends, our analyses are limited by the relatively small sample size.

Despite the foregoing limitations, we have clearly demonstrated a high rate of CMV reactivation after $CD34^+$-selected tandem APBSCT for MM. Preemptive anti-CMV therapy effectively prevented invasive CMV infection in our cohort and should be considered, especially when tandem transplantation with novel chemotherapeutics is planned. Ultimately, further studies are needed to determine whether the infectious risks of tandem transplantation outweigh the potential cancer-related benefits. In addition, prospective studies involving larger numbers of patients with MM are needed to better define the unique risk factors for CMV reactivation and invasive disease in the era of novel combination chemotherapy and tandem transplantation.

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